FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
ASZD-P01-210	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	
Not Yet Assigned 10/070211	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/GB00/03474	11 September 2000
PRIORITY DATE CLAIMED	
15 September 1999	

TITLE OF INVENTION

NOVEL COMPOUNDS

APPLICANT(S) FOR DO/EO/US

AstraZeneca UK Limited et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☒ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☒ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

PTO Form 1449; References AA - AG **; and return receipt postcard.**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5) Not Yet Assigned	INTERNATIONAL APPLICATION NO. PCT/GB00/03474	ATTORNEY'S DOCKET NUMBER ASZD-P01-210

10/070211

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1000.00		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$860.00		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$710.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	22 - 20 =	2	x $18.00	$36.00	
Independent claims	1 - 3 =	0	x $80.00	$0.00	
Multiple Dependent Claims **(check if applicable)**			☒	$270.00	
TOTAL OF ABOVE CALCULATIONS =				$1,016.00	
☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$1,016.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00	
TOTAL NATIONAL FEE =				$1,016.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00	
TOTAL FEES ENCLOSED =				$1,016.00	
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **18-1945** in the amount of **$1,016.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **18-1945** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

David P. Halstead
NAME

44,735
REGISTRATION NUMBER

February 26, 2002
DATE

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT (Under 37 CFR 1.97(b) or 1.97(c))	Docket No. ASZD-P01-210

In Re Application Of: **Barry Theobald**

Serial No.	Filing Date	Examiner	Group Art Unit
To be assigned	February 26, 2002	To be assigned	To be assigned

Title:

Novel Compounds

Address to:
Assistant Commissioner for Patents
Washington, D.C. 20231

37 CFR 1.97(b)

1. ☒ The Information Disclosure Statement submitted herewith is being filed within three months of the filing of a national application; within three months of the date of entry of the national stage as set forth in 37 CFR 1.491 in an international application; or before the mailing date of a first Office Action on the merits, whichever event occurs last.

Signature

Dated: **February 25, 2002**

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Customer ID 28120

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): AstraZeneca UK Limited et al.			Docket No. ASZD-P01-210
Serial No. Not Yet Assigned	Filing Date February 22, 2002	Examiner Not Yet Assigned	Group Art Unit N/A

Invention: NOVEL COMPOUNDS

I hereby certify that the following correspondence:

Transmittal Concerning a Filing Under 35 USC 371 (2 pgs); Copy of International Publication No: WO 01/19826 A2; Copy of IPER; Copy of Form PCT/IB/306; Copy of International Search Report; PTO Form 1449; Transmittal for Information Disclosure Statement; attached References; Certificate of Express Mail; and return receipt postcard.

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

February 26, 2002
(Date)

(Typed or Printed Name of Person Mailing Correspondence)

(Signature of Person Mailing Correspondence)

EL 805 319 606 US
("Express Mail" Mailing Label Number)

Note: Each paper must have its own certificate of mailing.

NOVEL COMPOUNDS

FIELD OF THE INVENTION

The present invention provides novel hydroxypyrrolidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

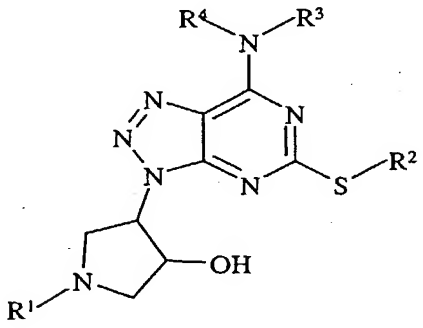
Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and platelet-mediated occlusion or re-occlusion also compromises angioplasty.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K. L. et. al. (1994) *Circulation* **90**, pp. 1638-1642).

It has been found that ADP acts as a key mediator of thrombosis. ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology,* (1994), **113**, 1057-1063, and Fagura et al., *Br. J. Pharmacology* (1998) **124**, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see *J. Med. Chem.* (1999) **42**, 213). There is a need to find P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

DESCRIPTION OF THE INVENTION

In a first aspect the invention provides a compound of formula (I):



(I)

wherein:

R^1 is H, CH_2R^5 or COR^6;

R^2 is alkyl C_{1-6} or alkenyl C_{1-6}, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen;

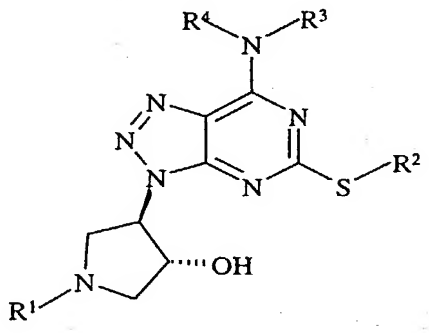
R^3 is cycloalkyl C_{3-8}, optionally substituted by R^7;

R^4 is H or alkyl C_{1-6}, optionally substituted by one or more halogens;

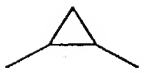
R^5 is H, phenyl or alkyl C_{1-6}, optionally substituted by halogen, OR^8, phenyl;
R^6 is OR^9 or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen, OR^{10}, phenyl;
R^7 is phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen, OR^8;
R^8, R^9 and R^{10}, are independently H or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen or alkyl C_{1-6};

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

Preferably the compound of formula (I) has the following stereochemistry:



(Ia)

Where R^3 is  the stereochemistry is preferably 

Preferably R^1 is H, CH_2Ph, CH_2CH_2OH, or CO_2tBu.
Preferably R^2 is n-Pr.
Preferably R^3 is cycloalkyl C_{3-8} substituted by phenyl.
Preferably R^4 is H or methyl.

Compounds of the invention include:

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*S*-[3α,4β(1*S**,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*R**, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*S**,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

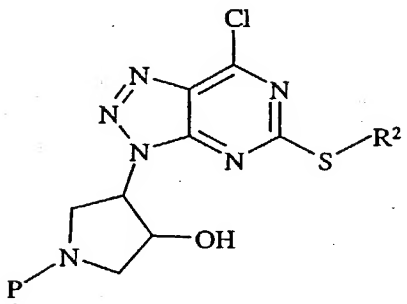
[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-(phenylmethyl)-3-pyrrolidinol;

[3*R*-[3α, 4β(1*R**,2*S**)]]-1-Acetyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

The invention further provides a process for the preparation of a compound of formula (I) which comprises:

a. For compounds of formula (I) where R^1 is H, reacting a compound of formula (II):

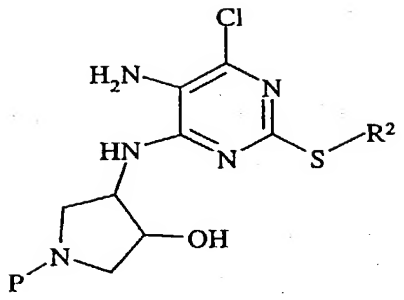


(II)

wherein R^2 is as defined above and P is a protecting group, preferably t-BuOCO, with R^3R^4NH, wherein R^3 and R^4 are as defined in (I), and a base, preferably triethylamine or *N,N*-diisopropylethylamine, in the presence of an inert solvent preferably acetonitrile, preferably at a temperature between about 20 °C and about 100 °C and optionally thereafter removing any protecting groups.

Examples of protecting groups include t-BuOCO and CH_2Ph. Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

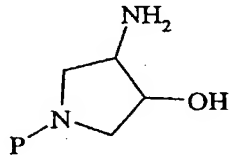
A compound of formula (II) can be prepared by diazotizing a compound of formula (III):



(III)

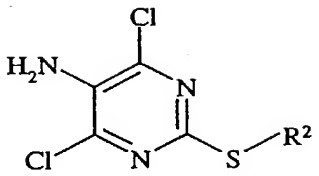
where R^2 and P are defined above, and where necessary other reactive groups might also be protected, with a C_{1-6} alkyl nitrite, preferably iso-amylnitrite in the presence of an inert solvent preferably acetonitrile at a temperature of between about 20 and about 80°C, or with an alkali metal nitrite, preferably sodium nitrite, under aqueous acidic conditions, preferably aqueous hydrochloric or acetic acid and preferably at a temperature between about 0°C and about 20°C.

A compound of formula (III) can be prepared by reacting a compound of formula (IV):



(IV)

wherein P is a protecting group, with a compound of formula (V):

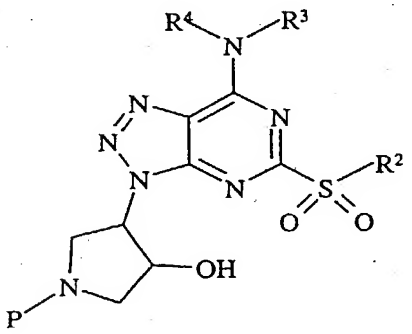


(V)

wherein R^2 is as defined in formula (I) and is preferably n-propyl. The reaction is carried out in the presence of a base, preferably triethylamine or *N,N*-diisopropylethylamine, in an inert solvent preferably *N,N*-dimethylformamide or n-butanol, at a temperature between about 100°C and about 150°C.

The preparation of the formula (IV) racemate is described in Okada et al., Chem. Pharm. Bull. (1993), **41**, 132-8; the preparation of formula (IV) enantiomers is described in Schaus, et al., J. Org. Chem. (1997), **62**, 4197-9; the preparation of a compound of formula V (R^2 is n-propyl) is described in EP 508687.

Compounds of formula (I) where R^2 is other than n-propyl are prepared by displacement of the sulphone group from a compound of formula (VI):



(VI)

where R^2 is n-propyl, P, R^3 and R^4 are defined above, using either a sodium alkylthiolate (R^2SNa) in the presence of an inert solvent, preferably *N,N*-dimethylformamide, preferably at a temperature between about 0°C and about 50°C or sodium hydrosulphide (NaSH), in the presence of an inert solvent preferably *N,N*-dimethylformamide. The latter reaction is followed by alkylation with an alkyl halide (R^2X, where X is a leaving group preferably bromide or iodide), preferably at a temperature between about 0°C and about 50°C and optionally thereafter removing any protecting groups.

The preparation of the compound of formula (VI), where R^2 is n-propyl, is preferably carried out by reacting a compound of formula (I), where R^1 has been protected as described above, with a peracid, preferably *m*-chloroperbenzoic acid, in the presence of an inert chlorocarbon solvent such as dichloromethane or a mixture of dichloromethane and methanol, at a temperature between about 0 °C and about 50 °C.

b. For compounds of formula (I) where R^1 is CH_2R^5, where R^5 is defined in formula (I), the reaction scheme outlined in a. above is followed by reductive amination using an aldehyde (R^5CHO) and a reducing agent, preferably sodium triacetoxyborohydride, and optionally thereafter removing any protecting groups. The reductive amination reaction is preferably carried out in the presence of an inert solvent preferably *N,N*-dimethylformamide, tetrahydrofuran or a mixture of acetonitrile and *N*-methylpyrrolidone and preferably at a temperature between about 0 °C and about 50 °C.

c. For compounds of formula (I) where R^1 is COR^6, where R^6 is defined in formula (I), the reaction scheme outlined in a. above is followed by acylation using an acid halide (R^6COX) or anhydride ($(R^6CO)_2O$) or an acid (R^6CO_2H) in the presence of a suitable activating agent preferably *N,N'*-carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide, and a base preferably triethylamine or *N,N*-diisopropylethylamine, and optionally thereafter removing any protecting groups. The acylation is preferably carried out in the presence of an inert solvent preferably dichloromethane, chloroform or tetrahydrofuran and preferably at a temperature between about 0 °C and about 50 °C.

Compounds of formula (II), (III), (IV) and (V) form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran, or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary revascularisation procedures including angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced

platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

In particular, the compounds of the invention are useful in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and stable and unstable angina, especially unstable angina.

The invention also provides a method of treatment or prevention of the above disorders which comprises administering to a patient suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to the invention.

According to the invention there is further provided the use of a compound according to the invention as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of the above disorders.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a

pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler. One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound. Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution, which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like.

Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol , mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak®, Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2)) was carried out using Fisher Matrix silica, 35-70 μm. For examples which show the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

[3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) (3*R*,4*R*)-3-[[5-Amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino]-4-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

Triethylamine (18.8ml) was added to a solution of (3*R*,4*R*)-4-amino-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester (prepared as described in J. Org. Chem., **1997**, *62*, 4197 using the (*S*,*S*)(salen)Cr(III)complex) (3.63g) and 4,6-dichloro-2-propylthiopyrimidine-5-amine (prepared as described in *EP508687*) (3.56g) and the resulting mixture was heated at 100°C for 24 hours. The excess triethylamine was removed *in vacuo* and the residue was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 97:3 as eluant) followed by trituration with diethylether/iso-hexane to give the subtitle compound (4.16g).

MS (APCI) 404 ($M+H^+$, 100%).

b) (3*R*,4*R*)-4-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

The product from step a) (4.1g) and iso-amylnitrite (2.74ml) were heated under reflux in acetonitrile (20ml) for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography (SiO_2, ethyl acetate:iso-hexane, 1:4 as eluant) to afford the sub-title compound (3.32g).

MS (APCI) 415 ($M+H^+$, 100%).

c) [3*R*-[3α,4β(1*R,2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

N,N-diisopropylethylamine (3ml) was added to a solution of the product from step b) (1.2g) and (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R*, R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L. A. Mitscher *et al.*, J. Med. Chem., **1986**, *29*, 2044) (1.23g) in dichloromethane (40ml). The reaction mixture was stirred at room temperature for 16 hours then washed with water. The organic phase was washed with dilute hydrochloric acid and brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 99:1 as eluant) to afford the sub-title compound (1.12g).

MS (APCI) 512 ($M+H^+$, 100%).

d) [3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

The product from step c) (0.54g) was dissolved in trifluoroacetic acid (22.5ml) and water (2.5ml) and the solution stirred at room temperature for 4h. The solvents were evaporated and the residue dried by azeotropic distillation with toluene (4x50ml) followed by methanol (50ml) to give a yellow foam. The crude product was triturated with diethylether (50ml) to afford a white powder that was recrystallised (ethyl acetate) to afford the title compound (0.37g) as a white solid.

MS (APCI) 412 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.5 (2H, br s), 9.47 (1H, d), 7.10-7.35 (5H, m), 6.28 (1H, d), 5.26 (1H, br m), 4.65 (1H, br s), 3.90 (2H, m), 3.52 (1H, d,AB), 3.3 (1H, m), 3.24. (1H, m), 2.8-3.0 (2H, t,AB), 2.13 (1H, m), 1.54 (1H, d,t), 1.47 (2H, sext.), 1.34 (1H, br q), 0.79 (3H, t).

Example 2

[3*S*-[3α,4β(1*S,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

a) (3*S*,4*S*)-3-[[5-Amino-6-chloro-2-(propylthio)pyrimidin-4-yl]amino]-4-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

Prepared according to the method of Example 1, step a) using (3*S*,4*S*)-4-amino-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester (prepared as described in J. Org. Chem., **1997**, *62*, 4197 using a(*R*,*R*)(salen)Cr(III)complex).

MS (APCI) 404/406 ($M+H^+$), 404 (100%).

b) (3*S*,4*S*)-4-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-hydroxy-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester

Prepared according to the method of Example 1, step b).

MS (APCI) 315 ($M+H-BOC^+$, 100%).

c) [3*S*-[3α,4β(1*S,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

Prepared according to the method of Example 1, step c).

MS (APCI) 512 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.40 (1H, d), 7.31-7.27 (2H, m), 7.20-7.15 (3H, m), 5.78-5.76 (1H, m), 5.11-5.06 (1H, m), 4.61-4.56 (1H, m), 3.94-3.81 (2H, m), 3.69-3.62 (1H, m), 3.30-3.18 (2H, m), 3.11-2.80 (2H, m), 2.15-2.10 (1H, m), 1.73-1.23 (13H, m), 0.80 (3H, t).

Example 3

[3*S*-[3α,4β(1*R, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

a) [3*S*-[3α,4β(1*R, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester**

Prepared according to the method of Example 2, step c) using (1*S*-*trans*)-2-phenylcyclopropanamine, [*S*-(*R**, *R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L. A. Mitscher *et al.*, J. Med. Chem., **1986**, *29*, 2044).

MS (APCI) 512 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.40 (1H, d), 7.31-7.27 (2H, m), 7.20-7.15 (3H, m), 5.78-5.76 (1H, m), 5.11-5.06 (1H, m), 4.62-4.58 (1H, m), 3.94-3.81 (2H, m), 3.69-3.63 (1H, m), 3.30-3.18 (2H, m), 3.11-2.80 (2H, m), 2.15-2.11 (1H, m), 1.72-1.23 (13H, m), 0.80 (3H, t).

Example 4

[3*S*-[3α,4β(1*S,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) [3*S*-[3α,4β(1*S,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

Prepared according to the method of Example 1, step d) using the compound of Example 2, step c)

MS (APCI) 412 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.5 (2H, br s), 9.48 (1H, d), 7.10-7.35 (5H, m), 6.30 (1H, d), 5.26 (1H, br m), 4.64 (1H, br s), 3.9 (2H, m), 3.5 (1H, d,AB), 3.26 (1H, m), 3.24. (1H, m), 2.7-3.0 (2H, t,AB), 2.11 (1H, m), 1.55 (1H, d,t), 1.46 (2H, sext.), 1.34 (1H, br q), 0.78 (3H, t).

Example 5

[3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) [3*R*-[3α,4β(1*R,2*S**)]]-3-Hydroxy-4-[7-[N-methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester.**

N,N-diisopropylethylamine (0.5ml) was added to a solution of the product from Example 1 step b) (0.3g) and (1*R-trans*)-*N*-methyl-2-phenylcyclopropylamine hydrochloride (prepared as described by C. Kaiser *et al*, J. Org. Chem., **1962**, *27*, 768-773, using (1*R-trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, *29*, 2044) (0.2g) in dichloromethane (20ml). The reaction mixture was stirred at room temperature for 48 hours then washed with water. The organic phase was washed with dilute hydrochloric acid and brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 99:1 as eluant) to afford the sub-title compound (0.36g).

MS (APCI) 470 ($M+H^+$, 100%).

b) [3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

A solution of the product from step a) (0.36g) in 9:1 trifluoroacetic acid:water (10ml) was stirred at room temperature for 2 hours. The solvent was removed and co-evaporated with toluene (3x). The residue was dissolved in water (20ml) and ethanol (1ml) and freeze-dried for 16 hours to give the title compound (0.33g).

MS (APCI) 426 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.33 (2H, br s), 7.29 (2H, m), 7.20 (3H, m), 6.04 (1H, br s), 5.27 (1H, m), 4.72 (1H, d), 3.84-3.97 (2H, m), 3.56 (4H, m), 3.31 (1H, d), 3.06 (3H, under DMSO), 2.43 (1H, under H_2O), 1.54-1.66 (3H, m), 1.45 (1H, m), 0.94 (3H, t).

Example 6

[3*R*-[3α,4β(1*R,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

a) [3*R*-[3α,4β(1*R,2*S**)]]-1-[2-[(1,1-Dimethylethyl)(dimethyl)silyl]oxy]ethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.**

[[(1,1-Dimethylethyl)dimethylsilyl]oxy]acetaldehyde (*Tet. Lett.*, **1995**, *36*, 6033) (0.27g) was added to a solution of the product from Example 1 step d) (0.4g) and sodium triacetoxyborohydride (0.48g) in dry tetrahydrofuran (10ml) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (thrice). The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 99:1 as eluant) to give the sub-title compound (0.2g).

MS (APCI) 570 ($M+H^+$, 100%).

b) [3*R*-[3α,4β(1*R,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol, trifluoroacetate salt**

Tetrabutylammonium fluoride hydrate (0.2g) was added to a solution of the product from step a) (0.2g) in dry tetrahydrofuran (10ml) and the mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by chromatography (SiO_2, dichloromethane:methanol, 95:5 as eluant). Trifluoroacetic acid (22μl) was added to a solution of the resulting oil in diethylether (5ml) and the solid formed was collected by filtration to give the title compound (0.12g).

MS (APCI) 456 ($M+H^+$, 100%).

NMR δH (d_6-DMSO+D_2O) 7.31 (2H, m), 7.21 (3H, m), 5.36 (1H, br s), 4.87 (1H, br s), 4.18 (1H, m), 4.04 (1H, m), 3.82 (3H, m), 3.55 (1H, under H_2O), 3.45 (2H, m), 3.29(1H, br s), 3.02 (2H, br s), 2.22 (1H, br s), 1.58 (2H, br s), 1.50 (1H, m), 1.36 (1H, m), 0.88 (3H, br s).

Example 7

[3*R*-[3α,4β(1*R,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-(phenylmethyl)-3-pyrrolidinol, trifluoroacetate salt**

Benzaldehyde (0.1ml) was added to a solution of the product from Example 1 step d) (0.26g) and sodium triacetoxyborohydride (0.32g) in dry tetrahydrofuran (10ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (thrice). The combined organic phase was washed with brine, dried and concentrated. Trifluoroacetic acid (20μl) was added to a solution of the resulting oil in diethylether (5ml) and the solvent was removed *in vacuo*. The residue was dissolved in water (20ml) and ethanol (5ml) and freeze-dried for 16 hours. Purification by chromatography (HPLC, Novapak® C18 column, 0.1% aqueous trifluoroacetic

acid:acetonitrile, gradient elution 75:25 to 0:100 over 15 minutes), followed by freeze drying gave the title compound (0.094g).

MS (APCI) 502 ($M+H^+$, 100%).

NMR δH (d_6-DMSO+D_2O) 7.53 (2H, d), 7.48 (3H, m), 7.31 (2H, m), 7.20 (3H, m), 5.34 (1H, m), 4.88 (1H, m), 4.48 (2H, q), 4.05 (1H, m), 3.90 (1H, m), 3.72 (1H, m), 3.41 (1H, m), 3.30(1H, br m), 3.01 (2H, br m), 2.21 (1H, br s), 1.50-1.56 (3H, m), 1.36 (1H, m), 0.87 (3H, br s).

Example 8

[3*R*-[3α, 4β(1*R,2*S**)]]-1-Acetyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.**

A mixture of the product from Example 1 step d) (0.17g), acetic anhydride (0.046ml) and pyridine (0.078ml) in dichloromethane (3ml) was stirred at room temperature under a nitrogen atmosphere for 16 hours. The reaction mixture was diluted with water and extracted with dichloromethane (twice). The combined organic phase was washed with dilute hydrochloric acid and brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, dichloromethane:methanol, 98:2 as eluant) followed by trituration with acetonitrile to give the title compound (0.06g).

MS (APCI) 454 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.39 (1H, m), 7.30 (2H, m), 7.19 (3H, m), 5.77-5.86 (1H, m), 5.09-5.16 (1H, m), 4.60-4.69 (1H, m), 4.00-4.13 (1H, m), 3.91 (2H, m), 3.46, 3.68 (1H, m), 3.21 (1H, br m), 2.82-2.91 (2H, m), 2.13 (1H, m), 1.98 (3H, d), 1.34-1.54 (4H, m), 0.79 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$)-receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2-inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 µl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 µl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 µl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 µl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows.

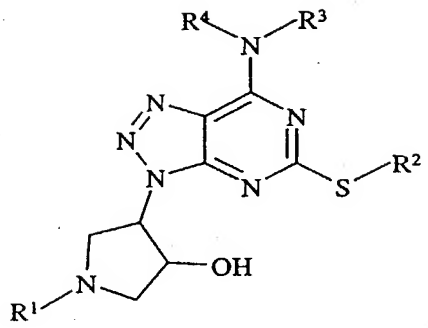
Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX were used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 µl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 µl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is H, CH_2R^5 or COR^6;

R^2 is alkyl C_{1-6} or alkenyl C_{1-6}, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen;

R^3 is cycloalkyl C_{3-8}, optionally substituted by R^7;

R^4 is H or alkyl C_{1-6}, optionally substituted by one or more halogens;

R^5 is H, phenyl or alkyl C_{1-6}, optionally substituted by halogen, OR^8, phenyl;

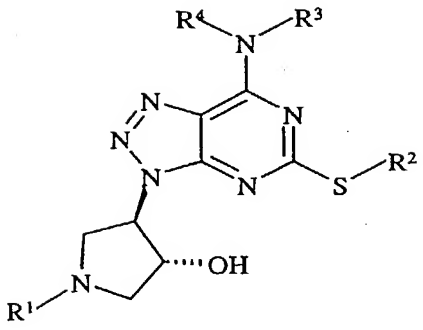
R^6 is OR^9 or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen, OR^{10}, phenyl;

R^7 is phenyl, optionally substituted by one or more groups selected from alkyl C_{1-6}, halogen, OR^8;

R^8, R^9 and R^{10}, are independently H or alkyl C_{1-6}, optionally substituted by one or more groups selected from halogen or alkyl C_{1-6};

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt

2. A compound according to claim 1 which is:



(Ia)

where R^1, R^2, R^3 and R^4 are as defined in claim 1.

3. A compound according to claim 2 in which R^3 is  where R^7 is as defined in claim 1.

4. A compound according to any one of claims 1 to 3 in which R^1 is H, CH_2Ph, CH_2CH_2OH, or CO_2tBu.

5. A compound according to any one of claims 1 to 4 in which R^2 is n-Pr.

6. A compound according to any one of claims 1 to 5 in which R^3 is cycloalkyl C_{3-8} substituted by phenyl.

7. A compound according to any one of claims 1 to 6 in which R^4 is H or methyl.

8. A compound according to claim 1 which is:
[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*S*-[3α,4β(1*S**,2*R**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*R**, 2*S**)]]-3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-pyrrolidinecarboxylate, 1,1-dimethylethyl ester;

[3*S*-[3α,4β(1*S**,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[*N*-Methyl-*N*-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-1-Hydroxyethyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol;

[3*R*-[3α,4β(1*R**,2*S**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-1-(phenylmethyl)-3-pyrrolidinol;

[3*R*-[3α, 4β(1*R**,2*S**)]]-1-Acetyl-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-3-pyrrolidinol.

Or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

10. A pharmaceutical composition for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, comprising a compound according to any one of claims 1 to 8.

11. A pharmaceutical composition for use in the treatment or prevention of unstable or stable angina, comprising a compound according to any one of claims 1 to 8.

12. A compound according to any one of claims 1 to 8 for use in therapy.

13. A compound according to any one of claims 1 to 8 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

14. A compound according to any one of claims 1 to 8 for use in the treatment or prevention of unstable or stable angina.

15. The use of a compound according to any one of claims 1 to 8 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

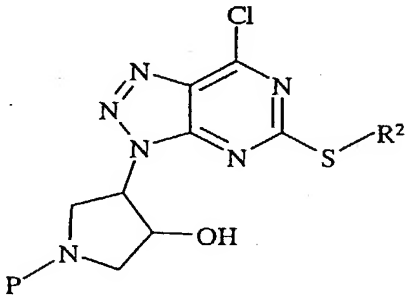
16. The use of a compound according to any one of claims 1 to 8 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of unstable or stable angina

17. A method of treatment or prevention of a platelet aggregation disorder which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of compound according to any one of claims 1 to 8.

18. A method of treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to any one of claims 1 to 8.

19. A method of treatment or prevention of unstable or stable angina, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to any one of claims 1 to 8.

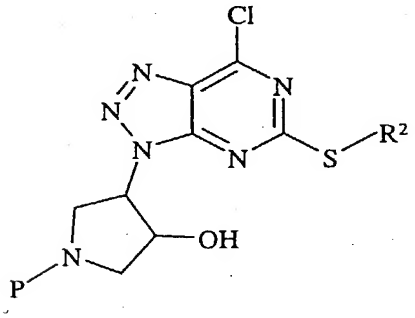
20. A process for the preparation of a compound of formula (I), where R^1 is H, which comprises reacting a compound of formula (II):



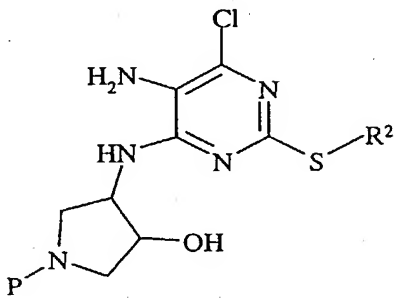
(II)

wherein R^2 is as defined in claim 1 and P is a protecting group, with R^3R^4NH, wherein R^3 and R^4 are as defined in claim 1, and a base and optionally thereafter removing any protecting groups.

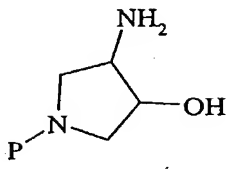
21. Compounds of formula (II), (III), (IV) and (V):



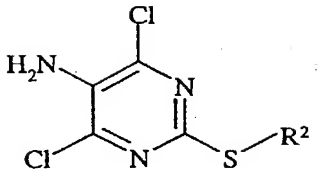
(II)



(III)



(IV)



(V)

wherein R^2 is as defined in claim 1 and P is a protecting group.

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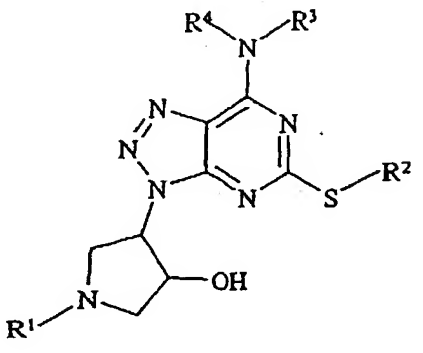

(I)

(57) Abstract: Compounds of the formula (I) and their use as anti-platelet aggregation compounds.

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10070211 , 020302

DECLARATION FOR UTILITY PATENT APPLICATION

Docket Number: ASZD-P01-210

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL COMPOUNDS

a patent application , the specification of which (check one)

☐ is attached hereto.
☒ was filed on February 26, 2002 , as United States Application Number 10/070,211 and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in Title 37, Code of Federal Regulation, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
9903290-6 (Number)	Sweden (Country)	September 15, 1999 (Day/Month/Year Filed)	☒ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States Provisional application(s) listed below.

(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Number)	(Filing Date)	(Status: patented, pending, abandoned)
PCT/GB00/03474		

I hereby appoint Madeline F. Baer, Reg. No. 36,437; J. Steven Baughman, Reg. No. 47,414; Johnny Y. Chen, Reg. No. 46,614; Gregory G. Glover, Reg. No. 34,173; William G. Gosz, Reg. No.: 27,787, Patricia Granahan, Reg. No. 32,227; David P. Halstead, Reg. No. 44,735; Daniel Hansburg, Reg. No. 36,156; Edward J. Kelly, Reg. No. 38,936; Charles Larsen, Reg. No. 48,533; Agnes S. Lee, Reg. No. 46,862; Paul E. Lewkowicz, Reg. No. 44,870; Yu Lu, Reg. No. P-50,306; Christopher T. Natkanski, Reg. No. P-50,365; Robert A. Mazzarese, Reg. No. 42,852; Spencer Schneider, Reg. No. 45,923; Sanjay Sitlani, Reg. No. 48,489; Wolfgang Stutius, Reg. No. 40,256; Matthew P. Vincent, Reg. No. 36,709; as attorneys/agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's signature: B. Teobald. Date: 10-5-02

Residence: Loughborough, Leicestershire, United Kingdom Citizenship: United Kingdom

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GBX